REMARKS

Upon entry of the foregoing amendment, claims 1-9, 11, and 13-34 are pending for the Examiner's consideration, with claims 1, 11, 13, 18, 29, and 33 being the independent claims. Claims 10 and 12 are cancelled herein without prejudice to or disclaimer of the subject matter contained therein. Independent claims 1, 11, 13, and 29 have been amended herein to recite that the microparticles comprise a polymeric binder. A conforming amendment to dependent claim 22 has also been made. Applicants submit that the foregoing amendments introduce no new matter. In this regard, the Examiner is referred to, for example, pages 8-9 of the application as originally filed.

Description of the Invention

As explained on page 8 of the application as originally filed, the present invention relates to injectable compositions having improved injectability, and to methods for the preparation of such injectable compositions. The injectable compositions of the present invention overcome injectability problems, particularly injectability failures that occur upon injection into muscle or subcutaneous tissue. Such injectability failures will be referred to herein as "*in vivo* injectability failures." *In vivo* injectability failures often manifest themselves in the form of a plug at the tip of the needle, and occur immediately or shortly after injection has been initiated. *In vivo* injectability failures are typically not predicted by laboratory or other *in vitro* testing.

The inventors have unexpectedly discovered that injectability is improved, and *in vivo* injectability failures significantly and unexpectedly reduced, by ***increasing*** the viscosity of the fluid phase of an injectable suspension. This is in contrast to conventional teachings that an increase in the viscosity hinders injectability and syringeability. As explained on pages 2-3 of the application as originally filed, viscosity is typically kept low, in order to facilitate mixing, resuspension of the particles with the vehicle, and to make the suspension easier to inject (*i.e.*, low force on the syringe plunger). Conventional parenteral suspensions are dilute, with limitations for viscosity because of syringeability and injectability constraints. *See*, for example, the Floyd, *et al.* Chapter referred to on page 2 of the application as originally filed.

Viscous vehicles, however, are not optimal for preparing homogeneous suspensions of microparticles because of the relative inability of viscous vehicles to penetrate and wet out a mass of dry particles. Suspensions prepared with viscous vehicles are prone to clump irreversibly. Consequently, such suspensions are not injectable via needles of medically acceptable size. A further disadvantage of viscous suspensions is the lack of ease of transferring such suspensions from the vial or container used to prepare the suspension to the syringe used for injection.

The present invention also solves the additional problems that arise from use of a viscous injection vehicle. In accordance with the present invention, microparticles are suspended in an injection vehicle having suitable wetting characteristics. The viscosity of the fluid phase of the injectable suspension is increased prior to injecting the suspension in order to improve injectability, and to reduce *in vivo* injectability failures.

Rejections Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1-7, 11, 13, 17, 19-21, and 29-32 under 35 U.S.C. § 103(a) as being unpatentable over WO 97/44039. The Examiner has rejected claims 8, 9, 10, 12, 15, 16, 18, 22-28, 33, and 34 under 35 U.S.C. § 103(a) as being unpatentable over WO 97/44039 in view of WO 95/13799. Finally, the Examiner has rejected claim 14 under 35 U.S.C. § 103(a) as being unpatentable over WO 97/44039 in view of U.S. Patent No. 5,631,021. Applicants respectfully submit that none of the foregoing rejections can properly be maintained for at least the reason that none of the cited documents discloses or suggests the claimed two-step process whereby the microparticles are first mixed with an injection vehicle to "wet" them and form a suspension, and the suspension is then mixed with a viscosity enhancing agent to increase the viscosity of the fluid phase of the suspension. Nor does WO 97/44039 disclose or suggest use of microparticles that comprise a polymeric binder, as required by each independent claim, and, for the reasons discussed in more detail below, WO 97/44039 cannot properly be combined with WO 95/13799.

Claims 1-9, 11, 13-17, 19-24, 29-32

Each of independent claims 1, 11, 13, and 29 recites a multiple step process wherein dry microparticles are first mixed with an injection vehicle to form a first suspension. The first suspension is then mixed with a viscosity enhancing agent to form a second suspension, whereby viscosity of the fluid phase of the second suspension is increased to provide injectability through a needle of specified size. As discussed above and on page 8 of the application as originally filed, the inventors unexpectedly discovered that an increase in viscosity improves injectability. This is contrary to conventional teachings such as the Floyd *et al.* chapter, and WO 97/44039 cited by the Examiner, which states that experiments with ***less viscous*** carriers were initiated when oil suspensions proved difficult to take up in a syringe. However, as explained above and on page 8 of the application, it is difficult to prepare homogeneous suspensions of microparticles using highly viscous vehicles because of the relative inability of viscous vehicles to penetrate and wet out a mass of dry particles. Instead, they prone to clump irreversibly, and are not injectable via needles of medically acceptable size. Therefore, the microparticles are first suspended in an injection vehicle having suitable wetting characteristics, and then the fluid phase of the suspension is increased prior to injecting the suspension in order to improve injectability, and to reduce *in vivo* injectability failures.

None of the documents cited by the Examiner discloses or suggests mixing dry microparticles to form a first suspension, and then mixing the first suspension with a viscosity enhancing agent to form a second suspension, with the viscosity of the fluid phase of the second suspension providing injectability through a needle of specified size. The Examiner recognizes that WO 97/44039 "does not teach mixing the ingredients in the claimed order," citing to page 7, lines 19-29 of that document. Page 7, lines 19-29 of WO 97/44039 states that the process of preparing the aqueous suspensions includes a number of steps, including "dispersing the active ingredient in the mixture while stirring, ***followed by*** homogenizing the mixture." The "mixture" referred to is the fluid phase of the suspension, and WO 97/44039 teaches homogenizing the mixture as the last step - it follows dispersing the active ingredient in the mixture.

As such, the teachings of WO 97/44039 are directly contrary to the claimed invention whereby the dry microparticles are first suspended with an injection vehicle, which step allows the microparticles to form a homogeneous suspension, and then the viscosity of the injection vehicle is increased to provide injectability. Therefore, Applicants respectfully submit that WO 97/44039 teaches away from the claimed invention, and, as such, it would not have been obvious to one skilled in the art to modify the order of mixing the ingredients by "routine experimentation" to obtained the claimed invention. For at least the foregoing reason, Applicants respectfully submit that the rejection based on WO 97/44039 cannot properly be maintained.

Claims 1-9, 11, 13-34

Every independent claim presented herein requires that the microparticles comprise a polymeric binder. As recognized by the Examiner on page 3 of the Office Action, WO 97/44039 "does not teach binder in the particle." In an attempt to remedy this deficiency, the Examiner refers to WO 95/13799, which teaches a process for preparing biodegradable microparticles comprising a biodegradable polymeric binder and a biologically active agent, such as risperidone. However, Applicants respectfully submit that the teachings of WO 97/44039 and WO 95/13799 cannot properly be combined.

There is no motivation to combine the teachings of WO 97/44039 with WO 95/13799 to add a polymeric binder for the following reasons. First, WO 97/44039 is specifically directed to a sustained or delayed release formulation of a metabolite or pro-drug of risperidone, while WO 95/13799 is directed to sustained-release microparticles of risperidone itself. WO 97/44039 explicitly states that "the problems associated with the genetic polymorphism in the metabolism of risperidone to its active metabolite 9-hydroxyrisperidone can possibly be avoided by administration of the metabolite or a long-acting prodrug thereof, ***instead of risperidone itself*** (page 2, lines 30-33; emphasis added). Because WO 97/44039 teaches away from use of risperidone itself, which is the active agent used in WO 95/13799, one skilled in the art would not combine the teachings of the two documents in the manner suggested by the Examiner.

Second, there would be no reasonable expectation of success to substitute risperidone encapsulated in a biodegradable and biocompatible polymer for the crystalline form of the metabolite. As described on page 4, lines 1-9 of WO 97/44039, the basic requirements of the depot formulation include plasma levels above a minimal therapeutic concentration but below a side-effect producing threshold value. The plasma levels are a function of the release rate of the active ingredient, which will be very different between a crystalline form of the metabolite and a polymer-encapsulated form of the drug itself. That the release rate is markedly different between a crystalline form and an encapsulated form is evidenced by the statement in U.S. Patent No. 6,555,544 ("the '544 patent" previously cited by the Examiner) that the formulations of WO 97/44039 are far too long-lasting in humans to be therapeutically useful. *See* Column 2, Lines 23-27 of the '544 patent. For at least the foregoing reasons, Applicants respectfully submit that WO 97/44039 and WO 95/13799 cannot properly be combined, and, as such, the rejection based upon the combination cannot properly be maintained.

For at least all of the reasons discussed above, Applicants respectfully submit that the rejections under 35 U.S.C. § 103(a) cannot properly be maintained.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete response has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment is respectfully requested.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

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Respectfully submitted,

By

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